Clear Cell Neoplasms of Salivary Glands: A Diagnostic Challenge

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Abstract: This review focuses on the heterogeneous group of clear cell neoplasms of salivary glands and attempts to identify major differential diagnostic features. Within the head and neck region, clear cells are found most commonly in salivary gland tumors, but may also be seen in tumors of squamous or odontogenic epithelial origin, primary or metastatic carcinomas, benign or malignant melanocytic lesions, or benign or malignant mesenchymal tumors. Clear cells occur fairly commonly among a wide variety of salivary gland neoplasms, but mostly they constitute only a minor component of the tumor cell population. Clear cells represent a major diagnostic feature in two salivary gland neoplasms, epithelial-myoepithelial carcinoma and hyalinizing clear cell carcinoma. In addition, salivary gland neoplasms composed predominantly of clear cells could also include clear cell variants of other salivary neoplasms, such as mucoepidermoid carcinoma and myoepithelial carcinoma, but their tumor type-specific histologic features may only be available in limited nonclear cell areas of the tumor. Diagnosing predominantly clear cell salivary gland tumors is difficult because the immunoprofile and morphologic features may overlap and the same tumor entity may also have a wide range of other histologic presentations. Many salivary gland tumors are characterized by tumor type-specific genomic alterations, particularly gene fusions of the ETV6 gene in secretory carcinoma, the MYB and MYBL1 genes in adenoid cystic carcinoma, the MAML2 gene in mucoepidermoid carcinoma, the EWSR1 gene in hyalinizing clear cell carcinoma, and others. This review focuses on the diagnostic challenge in two salivary gland neoplasms, EMC and CCC. In addition, salivary gland neoplasms composed predominantly of clear cells could also include clear cell variants of well-defined salivary neoplasms such as MEC, MC, myoepithelioma, and oncocytoma, but their specific histologic features can be hidden and only apparent in a limited nonclear cell component of the tumor.

Key Words: clear cell neoplasm, salivary gland, hyalinizing clear cell carcinoma, epithelial-myoepithelial carcinoma, metastatic clear cell carcinoma, odontogenic

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Diagnosing predominantly clear cell salivary gland tumors is difficult because many different tumor types may share similar morphologic features, and the same tumor entity may have a wide range of other histologic presentations (Table 1). Moreover, the immunoprofiles of predominantly clear cell salivary gland tumors of different entities may overlap, such as p63/p40/HMW cytokeratin positive and S100/SOX10 negative immunostaining in hyalinizing CCC, MEC, and squamous cell carcinoma (SCC).5

Over the past decade, a significant development in molecular techniques and understanding of the genomic landscape of salivary gland neoplasms has taken place.6-8 Several salivary gland tumors were characterized by recurrent genomic alterations, including gene fusions involving the ETV6 gene in secretory carcinoma,9,11 the MYB and MYBL1 genes in AdCC,12 the MAML2 gene in MEC,13,14 and the fusion EWSR1::ATF1 in hyalinizing CCC.15 In addition, HRAS exon 3 mutations were seen in most cases of EMC,16 and rearrangement of the gene EWSRI was described in a significant proportion of clear cell MCs,17,18 respectively. Thus, along with conventional histologic examination and immunoprofiling, molecular and genetic tests can facilitate the diagnosis of salivary gland clear cell tumors by demonstrating genetic alterations specific to them.

### MAJOR PRIMARY CLEAR CELL NEOPLASMS OF SALIVARY GLANDS

#### Hyalinizing Clear Cell Carcinoma

Hyalinizing CCC is a low-grade salivary gland malignancy that was originally described by Batsakis in 1980,19 and the concept was later refined by Simpson et al20 and Milchgrub et al.21 While it is possible that hyalinizing CCC rarely arises also in major salivary glands, it occurs most commonly in minor salivary glands, usually in the palate or the base of the tongue22 (Fig. 1). Until recently, hyalinizing CCC was regarded not as a distinct entity but rather as a diagnosis of exclusion. Uncertainty about the true nature and identity of hyalinizing CCC was reflected in the frequently changing designations of this tumor type. Originally described as “clear cell carcinoma,”19,20 it was later designated as “hyalinizing clear cell carcinoma.”21 Then, in the 2005 World Health Organization Classification (WHO) of Head and Neck Tumors it was renamed as “clear cell carcinoma, not otherwise specified.”22,23 and in the 2008 Armed Forces Institute of Pathology Fascicle of Salivary Gland Tumors as “clear cell adenocarcinoma.”24 The term “clear cell carcinoma” then reappeared in the 2017 WHO Classification of Head and Neck Tumors,24 and finally the neoplasm is called “hyalinizing clear cell carcinoma” again in the upcoming 5th edition of WHO classification in 2022.25

The discovery that most hyalinizing CCCs harbor EWSR1::ATF1 fusion that is not found in any other type of salivary gland tumor, strongly supports the present view that hyalinizing CCC is a distinct tumor entity.12 Microscopically, hyalinizing CCC is typically composed of clear cells, arranged in anastomosing trabeculae, cords, nests, or solid sheets surrounded by a stroma of spindle-shaped fibroblasts and dense hypocellular hyalinized tissue sometimes with myxoid foci (Fig. 2). Hyalinizing CCCs have invasive borders, even occasionally exhibiting perineural infiltration, and the tumor cells display minimal nuclear pleomorphism with a very low mitotic and proliferative index. Histologically, there is a relatively wide range of appearances of hyalinizing CCC tumor cells; while a predominance of clear cells is seen in most examples, sometimes a variable proportion of the tumor cells may have pale eosinophilic rather than clear cytoplasm. Generally,

#### TABLE 1. Key Morphologic, Immunohistochemical, and Molecular Findings in Differential Diagnosis of Clear Cell Neoplasms of Salivary Glands

<table>
<thead>
<tr>
<th>Morphology</th>
<th>Immunoprofile</th>
<th>Molecular Profiling</th>
</tr>
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<tbody>
<tr>
<td>Hyalinizing CCC</td>
<td>Cytokeratin+, p63+, SMA-, calponin- S-100-, SOX10-</td>
<td>EWSR1::ATF1 EWSR1::CREM</td>
</tr>
<tr>
<td>Epithelial-myoepithelial carcinoma</td>
<td>CK7+ in epithelium; p63+, SMA+, calponin+, SMHC+, S-100+ in myoepithelium</td>
<td>HRAS codon 61 mutations</td>
</tr>
<tr>
<td>Myoepithelial carcinoma</td>
<td>Varibly p40+, p63+, SOX10-, S-100+, MSA+, SMA+, cytokeratin+</td>
<td>EWSR1 rearrangements and mutations</td>
</tr>
<tr>
<td>Mucoepidermoid carcinoma</td>
<td>p63+, p40+, S-100-, SOX10-</td>
<td>PLAG1 fusions with variable partners</td>
</tr>
<tr>
<td>Oncocytoma</td>
<td>p63+ in basal-like cells</td>
<td>EWSR1::ATF1 EWSR1::CREB EWSR1::CREM</td>
</tr>
<tr>
<td>Clear cell odontogenic carcinoma (CCOC)</td>
<td>Cytokeratin+, p63+, SMA-, calponin- S-100- p40+, p63+</td>
<td>Multiple somatic mutations, esp. TP53 mutations</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>Melan A+, S-100+, cytokeratin-</td>
<td>BRAF mutations</td>
</tr>
<tr>
<td>Malignant melanoma</td>
<td>RCC+, CD10+, vimentin+, CK7-, p63-</td>
<td>Multiple somatic mutations</td>
</tr>
<tr>
<td>Metastatic renal cell carcinoma</td>
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CCC indicates clear cell carcinoma.
however, many hyalinizing CCCs display a mixture of both cell types. Tumors with virtually no clear cells can occasionally be seen, but they usually retain the same overall growth pattern as typical clear cell examples of hyalinizing CCC. A very characteristic feature of hyalinizing CCC is the appearance of the stroma comprising abundant hyalinized basement membrane-like material. It is often sharply demarcated from the desmoplastic or fibrocellular stroma.
that sometimes appears myxoid and may mimic a PA. The presence of these two stroma types is essentially pathognomonic for the diagnosis of hyalinizing CCC and is seen in most, but not all cases. The finding of hyalinized stroma in a tumor with a cribriform architecture may mimic other more common salivary gland tumors, such as AdCC and PA, particularly if the hyalinizing CCC has only a minor clear cell component.

The presence of a diagnostic molecular marker, the EWSR1::ATF1 fusion, in hyalinizing CCC has allowed for a more complete appreciation of its histologic spectrum. This, in turn, has disclosed pitfalls in diagnosing carcinomas with clear cell morphology on the basis of histology alone (Fig. 2). For example, hyalinizing CCC sometimes exhibits overt squamous differentiation, and they may not be hyalinized, and they may not even be dominated by clear cells. Thus, without molecular confirmation, the diagnosis of hyalinizing CCC would hardly be possible. Immunophenotypically hyalinizing CCC has similarities to SCC and MEC with positive immunostaining for high-molecular weight keratin and p63 and negative immunostaining for markers of myoepithelial differentiation. Focal mucinous differentiation is known to occur in up to 50% of cases of hyalinizing CCC. The distinction of hyalinizing CCC from clear cell MEC can be truly challenging, and hyalinizing

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FIGURE 2. Hyalinizing clear cell carcinoma with EWS1::ATF or EWS1::CREM fusion. A, Hyalinizing clear cell carcinoma with EWS1::ATF1 gene fusion shows solid-alveolar nests of uniform clear cells with round to oval nuclei and decent chromatin, separated by gently cellular and hyalinized septa. B, Tumor cells are positive for p63. C, Tumor cells are negative for S100 protein, peripheral nerves serve as positive control. D, The fusion joining of EWS1 gene exon 8 with ATF1 gene exon 4 is illustrated. Protein domains are depicted. E, The fusion joining of EWS1 gene exon 14 with CREM gene exon 6 is illustrated. Protein domains are depicted.
CCC may be misclassified as the more common MEC.\textsuperscript{27,28} In one recent study, the presence of an alternative EWSR1::CREM fusion in a salivary CCC with a very prominent mucinous component and an original diagnosis of MEC, finally convinced pathologists of a revised diagnosis of hyalinizing CCC.\textsuperscript{29} This is a critical distinction as a solid nested MEC would be classified as high-grade malignancy with a worse prognosis and more aggressive treatment, while hyalinizing CCC usually behaves as a low-grade tumor.

### Epithelial-Myoepithelial Carcinoma

EMC is a rare salivary gland malignancy that comprises about 1% to 2% of all salivary gland tumors and 2% to 5% of malignant salivary gland tumors.\textsuperscript{40} Initially described by Donath et al in 1972,\textsuperscript{31} EMC was likely recognized as early as 1956 and reported under a variety of names such as adenomyoepithelioma, clear cell adenoma, tubular solid adenoma, monomorphic clear cell tumor, glycogen-rich adenoma, glycogen-rich adenocarcinoma, and CCC.\textsuperscript{32–34}

EMC represents a typical example of a biphasic salivary gland neoplasm. Histologically, it is composed of a tubulobular to nested bilayered arrangement of inner (luminal) ductal cells, and outer (abluminal) myoepithelial cells. The ductal component is typically composed of small lightly eosinophilic cuboidal cells forming tubules. The abluminal myoepithelial component consists of larger polygonal cells, usually with clear cytoplasm. This outer layer in turn is surrounded by a basement membrane of varying thickness; this can be so marked that the predominant histologic appearance of the tumor becomes that of a pseudocellular hyaline mass with only scanty bilayered neoplastic ducts.\textsuperscript{35}

The vast majority of EMCs have low-grade cytomorphicologic features, but up to one-third may show perineural invasion.\textsuperscript{36} Angiolymphatic invasion and necrosis, which appear to correlate with local recurrence, are less frequent.\textsuperscript{36}

Most EMCs have a predominant clear cell abluminal myoepithelial layer with a well delineated luminal ductal non-clear cell component. A double-clear variant of EMC is rare (3.3%);\textsuperscript{36} in this subtype, the cytoplasm of both the epithelial and myoepithelial cells is clear, (hence “double-clear”), thus obviously making morphologic distinction from hyalinizing CCC difficult. However, while the clear cells of hyalinizing CCC may look similar to the clear cells in EMC, the latter will have, at least focally, also a population of small dark ductal epithelial cells and a clear cell abluminal component with myoepithelial phenotype. The latter population may be identified with actin, smooth muscle myosin heavy chain, calponin, p63, or (less specifically) S100 antibodies.\textsuperscript{36} EMC can on occasions lack clear cells altogether; then immunohistochemistry for CK7 and p63 will reveal an unexpected biphasic pattern in a challenging undiagnosed carcinoma, which is then rightfully recognized as EMC. One other pointer in differentiating EMC from hyalinizing CCC is that the former with its biphasic cell population occurs most frequently in the parotid gland, whereas hyalinizing CCC composed of one neoplastic cell type only usually arises in minor salivary glands, particularly the palate.

In distinguishing EMC from other salivary gland tumors with biphasic differentiation immunohistochemistry is of limited value. However, a molecular test that can lead to an accurate diagnosis of EMC is now available.\textsuperscript{16,33} Mutations in codon 61 of HRAS gene have been detected in a vast majority of EMC, independent of histologic variants, the anatomic location and clinicopathologic parameters.\textsuperscript{36,37} This genetic alteration was consistently lacking from the histologic mimics of EMC. Thus, the assessment of HRAS mutations can contribute to correct diagnosis of EMC in challenging histopathologic settings.

### CLEAR CELL VARIANTS OF WELL DEFINED SALIVARY NEOPLASMS

#### Clear Cell Mucoepidermoid Carcinoma

MEC is the most common type of salivary gland carcinoma and it is found in both the major and minor salivary glands. It is typically composed of varying numbers of epidermoid, intermediate, and mucin-producing cells. Rarely, clear cells predominate over the other cell types, and these most often represent intermediate cells; tumors where this occurs are termed the clear cell variant of MEC.\textsuperscript{38–40} This variant is almost exclusively composed of cells with abundant optically clear cytoplasm, only mild to moderate nuclear enlargement, and a nested growth pattern (Fig. 3). In the clear cell variant of MEC tumor cells containing cytoplasmic mucin are rare and difficult to discern. The clear cytoplasm of the tumor cells is stained by periodic acid-Schiff with some granularity indicating the presence of glycogen, while the mucinous cells are stained by periodic acid-Schiff even after diastase digestion indicating mucin.\textsuperscript{40} Intraacellular mucins are also stained blue by Alcian blue. Immunohistochemical positivity for p63 and p40 and negativity for S100 and SOX10 may be helpful in differential diagnosis between MEC and the clear cell variant of MC and myoepithelioma. However, the immunoprofile of hyalinizing CCC is identical to that of MEC. Approximately 60% to 80% of MECs harbor a tumor type-specific translocation t(11;19)(q21;p13) and its CRTC1::MAML2 fusion gene or a rare variant translocation t(11;15)(q21;q26) with CRTC3::MAML2 fusion.\textsuperscript{131,142} Among the various salivary gland tumors, CRTC1::MAML2 fusion is specific for MEC and it can be used in diagnostic workup (Fig. 3). In selected problematic cases, demonstration of MAML2 rearrangement is recommended to confirm the diagnosis of MEC, particularly in examples of the oncocytic or clear cell variants of MEC, or in differential diagnosis from PAs with extensive oncocytic or mucinous metaplasia.\textsuperscript{40,43,44} In such cases, demonstration of MAML2 rearrangement may be critical for the correct diagnosis. Obviously, only positive results are informative.

#### Clear Cell Myoepithelial Carcinoma

MC is a malignant salivary neoplasm that is almost exclusively composed of myoepithelial cells and has an invasive growth pattern.\textsuperscript{45} Most MCs occur in the parotid gland followed by the palate, and the submandibular gland.\textsuperscript{18,45} In earlier studies, MC was reported to account for <2% of all salivary gland malignancies,\textsuperscript{46,47} but currently the incidence of MC is suspected to be higher. This is mainly because MC is easily underrecognized given its broad histologic spectrum and overlapping morphologic features with other salivary gland tumors, benign or malignant.\textsuperscript{49} MC may arise in the context of a preexisting PA (MC ex-PA) or de novo, and it may affect major or minor salivary glands.

Microscopically, morphologic heterogeneity is a typical histologic feature of MC, with tumors mostly displaying a mixture of different cell types and growth patterns, and this spectrum includes a clear cell variant.\textsuperscript{17,18,49} The neoplastic myoepithelial cells in MC exhibit considerable variation, and although most tumors show a mixture of different cells, one type often predominates. Most commonly, this is the epithelioid cell type (79%), followed by spindle cells (19%), basaloïd-type cells with high nuclear to cytoplasmic ratio (15%), and plasmacytoid cells (15%). Clear cells as the predominant cell type are relatively rare (8%).\textsuperscript{45}

Myoepithelial cells in various salivary gland neoplasms commonly undergo clear cell transformation, for example,
in EMC, but the clear cell variant of myoepithelial carcinoma (CCMC) composed exclusively of neoplastic cells with water clear cytoplasm is rare. CCMCs are composed of compact nests of large polyhedral cells with abundant clear cytoplasm divided by fibrous septa (Fig. 4).

Histologically, the most characteristic feature of CCMC is its multinodular architecture and its zonal cellular arrangement. The latter consists of a hypercellular peripheral rim of tumor cells surrounding a hypocellular sometimes necrotic center of the tumor islands. These 2 features help differentiate MC from benign tumors like PA and myoepithelioma, and malignancies such as hyalinizing CCC. CCMC characteristically is stained variably positive with p40, p63, SOX10, S-100 protein, high-molecular weight cytokeratin, muscle specific actin, and alpha smooth muscle actin antibodies. Calponin, which is considered the most sensitive and specific marker of myoepithelial cells, is however, rarely expressed in CCMC.17

In the differential diagnosis of CCMC, hyalinizing CCC must be considered. This distinction is important since CCMC tends to behave more aggressively with a 50% recurrence rate and 40% metastatic rate.50 In one recent study, patients with CCMC developed distant and lymph node metastases in 33% and 24% of cases, respectively.18 Positive immunostaining for cytokeratin, p40, and p63 is shared by CCMC and hyalinizing CCC. Although the

FIGURE 3. Clear cell mucoepidermoid carcinoma. A, The tumor was composed predominantly of cells with large and watery clear cytoplasm although more classic areas of mucoepidermoid carcinoma in the form of cystic structures with mucous cells are present as well. B, The presence of scattered mucous cells is highlighted periodic acid-Schiff positivity, while clear cells showed loss of periodic acid-Schiff staining. C, p63 was positive predominantly positive in clear cells. D, The fusion joining of CRTCl gene exon 1 with MAML2 gene exon 2 is illustrated. Protein domains are depicted. The fusion joining of CRTCl gene exon 1 with MAML2 gene exon 2 is illustrated. Protein domains are depicted.

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immunoprofile may vary considerably between cases, the minimal requirement for diagnosis of MC of salivary gland is coexpression of cytokeratin/EMA, SOX10, S100 protein, and/or at least 1 other myoepithelial marker. EWSR1 gene rearrangement has been identified in approximately one-third of MCs, which have predominantly clear cell morphology and aggressive clinical behavior. However, it was reported recently that none of the MCs with EWSR1 rearrangement identified by FISH, showed an EWSR1 fusion transcript in sequencing, and consequently this type of EWSR1 abnormality in MCs may actually represent a passenger mutation with minor effect. The most common fusion transcripts in all subtypes of MC included FGFR1::PLAG1 and TGFBR3::PLAG1, and LIFR::PLAG1, CTNNB1::PLAG1, FGFR1::PLAG1, and CHCHD7::PLAG1, respectively.

Clear Cell Variant of Oncocytoma

Oncocytes are benign encapsulated neoplasms composed of large epithelial cells with abundant eosinophilic granular cytoplasm because of the accumulation of mitochondria (oncocyes). p63 positive basal-like cells are an obligate component in oncocytoma. Oncocytomas may be multifocal and bilateral and constitute ~1% of all salivary gland tumors with marked tendency for parotid gland involvement and a much lower occurrence in the minor glands. Clear cells may occasionally predominate in some lesions and may be attributed to intracytoplasmic glycogen deposition or to fixation artifact. Clear cell oncocytoma is composed almost entirely of oncocyes with clear cytoplasm. It is important to mention that clear cell oncocytoma of the salivary gland is a benign tumor with excellent prognosis, when compared with other salivary tumors with exclusively or predominantly clear cell features, which are mostly malignant.

NONSALIVARY CLEAR CELL NEOPLASMS IN DIFFERENTIAL DIAGNOSIS

Odontogenic Clear Cell Carcinoma

Antonescu et al reported a recurrent EWSR1::ATF1 fusion in hyalinizing CCC of minor salivary glands. Identi cal EWSR1 and ATF1 gene rearrangements have also been identified in clear cell odontogenic carcinoma (CCOC), providing molecular evidence for a link between hyalinizing CCC and CCOC. CCOC is an odontogenic carcinoma characterized by nests, sheets, and cords of clear cells in a fibrocellular or hyalinized stroma. These tumors develop in the jaw bones with three quarters occurring in the mandible, most frequently in the posterior body and lower ramus. EWSR1 rearrangements have been reported in over 80% of cases of CCOC. ATF1 is the most common fusion partner of EWSR1, while CREB1 and CREM have been found less frequently. CCOCs are histomorphologically and
immunohistochemically similar to salivary gland hyalinizing CCC, and the 2 tumor types share EWSR1 rearrangement suggesting that they share a related form of pathogenesis.\textsuperscript{15}

There are not any specific markers for odontogenic CCC. The differential diagnosis of CCOC includes other clear cell-rich gnathic neoplasms such as clear cell calcifying epithelial odontogenic tumor, amyloid-rich central odontogenic fibroma, and both primary and metastatic intraosseous salivary tumors such as intraosseous clear cell MEC.\textsuperscript{60} Metastatic tumors containing clear cells include most likely RCC, clear cell breast carcinoma or thyroid carcinoma and, therefore, in addition to clinical history, the immunomarkers RCC, CD10, PAX8, CAIX, GATA3, ER/PR, TTF-1 are useful to rule out metastatic tumors.\textsuperscript{61}

Primary Cutaneous Tumors With Clear Cell Morphology

Primary salivary SCC is very rare, and the diagnosis can only be established by excluding metastatic SCC. A clear cell variant of cutaneous SCC, also referred to as hydropic SCC, is a very rare variant of SCC with extensive hydropic changes of keratinocytes.\textsuperscript{62} The hydropic degeneration of neoplastic cells and the accumulation of intracellular fluid and not the accumulation of glycogen, lipid, or mucin, results in its clear cell appearance. All cases reported so far have been in the head and neck region with the mandible being the most common site.\textsuperscript{63} Other differential diagnoses of cutaneous origin may include clear cell acanthoma, clear cell hidradenoma, clear cell hidradenocarcinoma, trichoepithelioma, and pilar tumor. In the latter tumor the clear cells have a high content of cytoplasmic glycogen. These tumors are, however, found in to the skin and do not represent a major differential diagnostic problem with salivary clear cell tumors.

Clear Cell Malignant Melanoma and Other Soft Tissue Clear Cell Neoplasms

Clear cell sarcoma is an rare aggressive malignant neoplasm with morphologic and immunohistochemical similarities to malignant melanoma. Although both malignant melanoma and clear cell sarcoma display melanin pigment and melanocytic markers, the 2 disorders are genetically distinct.\textsuperscript{64} Cases of malignant melanoma may contain BRAF mutations,\textsuperscript{65} whereas clear cell sarcoma lacks this mutation\textsuperscript{66} and characteristically exhibits the reciprocal translocation t(12;22)(q13;q12) resulting in a rearrangement of the EWS RNA binding protein 1 (EWSR1) gene. Clear cell sarcomas of the head and neck are uncommon.\textsuperscript{67,68} Tumors arising from the salivary glands are extremely rare but have been described in the parotid and submandibular glands, respectively.\textsuperscript{64,69}

METASTATIC NEOPLASMS WITH CLEAR CELL MORPHOLOGY

Between 15% and 35% of all parotid gland tumors are malignant and 21% and 42% of these represent metastatic disease. The majority of metastatic parotid tumors are derived from skin malignancies of the head and neck, usually SCCs in 45% and melanomas in 37%, respectively. A carcinoma metastatic to salivary glands and originating from a primary tumor located below the clavicle is uncommon, but the kidney is one of the more common infracavicular primary sites of such tumors. The most common clear cell malignancy metastatic to the oral mucosa and the jaws is RCC. However, metastases of melanoma and malignant clear cell tumors of the prostate, bowel, thyroid, and liver must also be considered, and in the absence of clinical information, excluded with appropriate immunohistochemical markers. Distinguishing primary salivary tumors from metastatic tumors with clear cell features has important diagnostic, therapeutic, and decision-making considerations.

Metastatic Renal Cell Carcinoma

Several metastatic RCCs have been reported in salivary glands, and the discovery of a metastasis may be the first indication of a primary RCC.\textsuperscript{3,4} Although the similarity with primary hyalinizing CCC is in most cases minimal, occasionally distinguishing it or even clear cell oncocytoma from metastatic RCC in the salivary gland can be challenging. RCC is considerably more vascular and displays generally either solid growth or has a crowded nested pattern. Small capillaries may be evident in hyalinizing CCC, but in RCC, the vascular channels are often conspicuous, dilated, and even sinusoidal. Hemorrhage and hemosiderin are generally more prominent in metastatic RCC. The nuclei are larger and more atypical than in hyalinizing CCC, and there is never squamous differentiation, or the dual type of stroma of hyalinizing CCC. Nevertheless, both primary hyalinizing CCC and metastatic RCC may be glycogen positive, and they may have a solid, organoid growth pattern, exhibit infiltrative growth, have little cytologic atypia and few mitotic figures, and may be composed almost entirely of clear cells. Mucicarmine positivity would favor a salivary gland primary tumor, but primary hyalinizing CCC of salivary gland is usually negative for intracytoplasmic mucin as well. In addition, immunohistochemistry can help, as clear cell RCC rarely expresses CK7 and virtually never is positive for p63, which is almost always expressed in hyalinizing CCC.\textsuperscript{70} Overall, RCC usually presents a more heterogeneous architecture and is more vascular than primary salivary CCCs. The more pleomorphism and cytologic atypia, the less likely the tumor is a primary hyalinizing CCC. Despite this, in some cases, it may not be possible confidently to differentiate between primary and metastatic carcinoma, and a clinical and imaging evaluation for a renal primary tumor should be performed.\textsuperscript{3,4} Finally, it must never be forgotten that a metastatic RCC is always included in a list of clear cell sarcoma differential diagnosis.\textsuperscript{5,21}

CONCLUSION

Clear cell neoplasms of salivary glands are diagnostic challenges. They comprise a diverse group of benign and malignant tumors with variable clinicopathologic characteristics. The distinction between different tumors of this group and this differential diagnosis from metastatic disease is essential and can be facilitated by a combination of thorough clinical evaluation, histologic, immunohistochemical staining as well as molecular genetic characteristics in selected cases.

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REFERENCES


